

Fluoroquinolone Resistance Among *Neisseria gonorrhoeae* Isolates in Hawaii, 1990–2000

Role of Foreign Importation and Increasing Endemic Spread

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Objectives: In 1999, an increase in ciprofloxacin-resistant *Neisseria gonorrhoeae* isolates was identified in Hawaii, prompting initiation of investigative studies.

Goals: The goal of this study was epidemiologic evaluation of this increase.

Study: The authors conducted a review of laboratory data; case-series and case-control studies based on medical record review; and a prospective case-control study based on patient interviews.

Results: A total of 10.4% (21 of 201) of gonococcal isolates from Hawaii in 2000 were ciprofloxacin-resistant compared with <1.5% per year from 1990 to 1997. From medical record review for patients diagnosed with ciprofloxacin-resistant *N. gonorrhoeae* infection from 1990 to 1999, 59% were Asian/Pacific Islanders and 91% were heterosexual. From review of 1998 and 1999 sexually transmitted disease (STD) clinic medical records, patients with ciprofloxacin-resistant *N. gonorrhoeae* were more likely to report recent foreign travel or a sex partner with recent foreign travel than patients with ciprofloxacin-susceptible *N. gonorrhoeae* (6 of 12 vs. 10 of 117, $P < 0.001$), but 50% (6 of 12) acquired a ciprofloxacin-resistant strain locally from a partner with no recent travel. In 2000, 70% (7 of 10) of STD clinic patients with ciprofloxacin-resistant *N. gonorrhoeae* acquired their infection locally from partners with no reported recent travel.

Conclusions: Infections with ciprofloxacin-resistant *N. gonorrhoeae* are increasing and evolving in Hawaii.

GONORRHEA IS THE SECOND MOST commonly reported notifiable disease in the United States with 358,995 cases reported in 2000. Gonococcal infection has been shown to increase sexual transmission of HIV by 3- to 5-fold.¹ If gonorrhea is not successfully treated, potentially serious sequelae include pelvic inflammatory disease, which often leads to ectopic pregnancy and infertility, and neonatal conjunctivitis, which can lead to blindness in the newborn. Strains of *Neisseria gonorrhoeae* readily acquire resistance to antimicrobials by various mechanisms, including acquisition of plasmids and by genetic mutations. After the introduction of sulfanilamide for treatment of gonorrhea in the 1930s, sulfanilamide-resistant strains of *N. gonorrhoeae* became so prevalent by 1945 that this antimicrobial could no longer be used to

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treat gonococcal infections. During the 1970s and 1980s, the emergence and widespread dissemination of strains of *N. gonorrhoeae* resistant to penicillin, and subsequently tetracycline, necessitated abandoning these antimicrobials as treatment for gonorrhea in the United States.

Since 1993, fluoroquinolone antimicrobials such as ciprofloxacin, ofloxacin, and more recently levofloxacin have been recommended by the Centers for Disease Control and Prevention (CDC) as first-line treatment for gonococcal infections in the United States as a result of their effectiveness as safe, single-dose oral antimicrobials.² Gonococcal isolates resistant to the fluoroquinolone antimicrobials first emerged in Asia, where fluoroquinolones have been used to treat gonorrhea since the 1980s, and became endemic in several Asian countries during the 1990s.³ To monitor emerging antimicrobial resistance of gonococcal isolates in the United States, the CDC, together with 5 regional laboratories and selected sexually transmitted disease (STD) clinics, established the Gonococcal Isolate Surveillance Project (GISP) in 1986.⁴ GISP is a 26-city sentinel surveillance system in the United States for monitoring antimicrobial resistance in *N. gonorrhoeae*. In 2000, 0.4% of all GISP gonococcal isolates were resistant to fluoroquinolones, and 38.7% of patients seen at GISP STD clinics were treated for gonorrhea with a fluoroquinolone antimicrobial.⁵

Despite gonorrhea rates in Hawaii that were relatively low compared with the United States as a whole (40.7 vs. 129.9 cases per 100,000 persons, respectively, in 2000),⁵ in 1991, Hawaii was the first state where fluoroquinolone-resistant *N. gonorrhoeae* were identified in the United States.⁶ In 1999, an increase in fluoroquinolone-resistant *N. gonorrhoeae* in Hawaii prompted the Hawaii Department of Health and CDC to initiate an investigation.⁷ This report summarizes the findings of that investigation and subsequent studies.

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Materials and Methods

Identification of Isolates

We reviewed data from the Hawaii Department of Health on cases of gonorrhea reported from 1990 to 2000. Sources of gonorrhea reporting in Hawaii were contacted to ascertain methods of gonorrhea diagnostic testing. Laboratories performing antimicrobial susceptibility testing of the gonococcal isolates from Hawaii were identified. These laboratories included the Hawaii Department of Health State Laboratory Facility, the Seattle GISP Regional Laboratory, and the CDC Neisseria Reference Laboratory. Antimicrobial susceptibility testing records from these 3 sources were reviewed to identify Hawaii isolates with resistance (CipR*) or intermediate resistance (CipI†) to ciprofloxacin. Records of tests performed from May 1, 1994, to December 31, 2000, at the State Laboratory were available. For the Seattle GISP Regional Laboratory and the CDC Neisseria Reference Laboratory, records of isolates tested from January 1, 1990, to December 31, 2000, were available. All known isolates were tested for antimicrobial susceptibility.

Case-Series Medical Record Review

Case-patients were identified and their medical record was reviewed. A case-patient was defined as a person diagnosed between January 1, 1990, and December 31, 1999, at any medical facility in Hawaii with gonorrhea caused by a CipI or CipR gonococcal isolate. A presumptive case-patient was defined as a person identified as a direct sexual contact of a case-patient with CipI or CipR *N. gonorrhoeae* and who tested positive for gonorrhea within 14 days of the case-patient's diagnosis by a nonculture test, making susceptibility testing impossible. All medical records, including those that had been archived, were reviewed for case-patients seen at the Diamond Head Health Center STD and HIV Clinic. This is the only public STD clinic in Hawaii and is located on Oahu, the most populated island. Nonarchived medical records were reviewed for all other case-patients/presumptive case-patients. When available, data were also abstracted from the standardized forms used by public health personnel when interviewing patients diagnosed with gonorrhea. Information abstracted from the medical record and interview forms included: demographic information, sexual orientation, number of sex partners, symptoms, STD history, chlamydia and syphilis test results, history of antimicrobial use or foreign travel in the last 30 days, and history of a sex partner with foreign travel in the last 60 days.

Sexually Transmitted Disease Clinic Medical Record-Based Case-Control Study

To characterize risk factors for acquisition of CipI/R *N. gonorrhoeae*, we conducted a medical record-based case-control study. For case-patients, we selected the subset of patients from the case-series medical record review who were diagnosed with gonorrhea at the STD clinic between January 1, 1998, and September 30, 1999. All gonococcal specimens from the STD clinic in Hawaii are sent to the State Laboratory for culture and undergo anti-

microbial susceptibility testing. The STD clinic gonorrhea culture log was used to identify all STD clinic patients who had positive gonorrhea cultures during this identified timeframe. A case-patient was selected from this log based on documentation that the patient's *N. gonorrhoeae* isolate was CipI or CipR on antimicrobial susceptibility testing. If a patient was listed in the STD clinic gonorrhea culture log with a positive gonorrhea culture, and the patient's isolate was not identified as CipI or CipR on antimicrobial susceptibility testing, the patient was selected as a control-patient. Medical records were reviewed for all patients meeting the case-patient or control-patient definitions. Information abstracted from the records was the same as that previously noted for the case-series medical record review.

Sexually Transmitted Disease Clinic Prospective Case-Control Interviews

To further evaluate potential risk factors for acquiring CipI/R *N. gonorrhoeae* identified by the medical record-based case-control study, a prospective interview-based case-control study was conducted at the STD Clinic. All patients seen at the STD Clinic in Hawaii from January to December 2000 with suspected or culture-confirmed gonorrhea were interviewed. Patients with suspected gonorrhea included: patients with urethral Gram stains showing Gram-negative diplococci; patients with symptoms consistent with gonorrhea, including vaginal/penile discharge, dysuria, or both; and patients who were sexual contacts, in the preceding 30 days, of patients diagnosed with gonorrhea. Patients with suspected gonorrhea were interviewed at the time of the initial visit. Patients who did not have suspected gonorrhea, but who had a specimen collected for gonorrhea culture that was subsequently identified as positive at the State Laboratory, were contacted, asked to return to the clinic, and interviewed after the culture results were known.

Information collected during the interview included: demographic information, sexual orientation, number of sex partners, symptoms, antimicrobial use and travel history in the preceding 30 days, sexual contact with members of the active-duty U.S. military, and sexual contact with commercial sex workers. These questions were asked regarding behavior while in Hawaii and while traveling, if the patient reported any recent travel. In addition, the interviews included questions about the patient's knowledge regarding these same items for all reported sex partners.

A case-patient was defined as a patient seen and interviewed at the STD Clinic during 2000 who had a positive culture for *N. gonorrhoeae* that was determined to be CipI or CipR on testing at 1 of the 3 laboratories performing antimicrobial susceptibility testing on Hawaii gonococcal isolates. A control-patient was defined as a patient seen and interviewed at the STD Clinic during 2000 who had a positive culture for *N. gonorrhoeae* that was not identified as CipI or CipR on testing done at 1 of these 3 laboratories.

Statistical Analysis

For all studies, data were entered into EpiInfo 6.04c for analysis. Categorical variables were compared by case status using chi-squared test or Fisher exact test.

Results

Identification of Isolates

The number of cases of gonorrhea reported to the Hawaii STD Program steadily declined each year from 1990 to 1996. From 1996 to 2000, approximately 500 cases of gonorrhea were reported each year to the Hawaii STD Program. In 2000, 158 (33%) were

*Resistance to ciprofloxacin (CipR) is defined by the National Committee for Clinical Laboratory Standards (NCCLS) as a minimum inhibitory concentration (MIC) ≥ 1.0 $\mu\text{g/mL}$ by agar dilution, or as disk diffusion zone size ≤ 27 mm.

†Intermediate resistance to ciprofloxacin (CipI) is defined by NCCLS as an MIC of 0.125–0.5 $\mu\text{g/mL}$ by agar dilution or as a disk diffusion zone size of 28–35 mm.

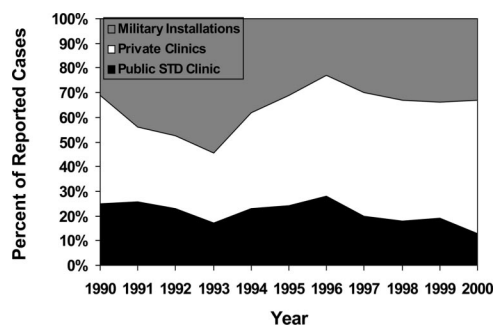


Fig. 1. Gonorrhea case-reporting by reporting source, Hawaii, 1990–2000.

reported from military installations, 261 (54%) were reported from private physicians and clinics, and 65 (13%) from the public STD Clinic (Fig. 1). Since October 1991, military installations in Hawaii have exclusively used nonculture testing for the laboratory diagnosis of gonorrhea. Excluding 1 laboratory belonging to a health maintenance organization, which used only culture, the private laboratories used a combination of nonculture testing and culture testing. Of the 484 gonorrhea cases reported in 2000, 201 (42%) were diagnosed by culture, all of which were tested for antimicrobial resistance. The remaining 283 (58%) were tested by nonculture methods at facilities other than the State Laboratory (military laboratories or private laboratories), and therefore gonococcal isolates were not obtained for antimicrobial susceptibility testing.

Hawaii State Laboratory records of total number of positive gonorrhea cultures were available for 1993 to the present. From January 1, 1993, to December 31, 2000, 124 CipI or CipR Hawaii gonococcal isolates were identified. Of these, 48 (39%) were CipI and 76 (61%) were CipR. The percentage of all cultured gonococcal isolates that were CipI increased slowly from 1993 to 1998 (Fig. 2). The percentage of gonococcal isolates that were CipI subsequently declined in 1999 and 2000. From 1993 to 1997, less than 1.5% of gonococcal isolates each year were CipR. In 1998, 16 (6.3%) of 256 isolates were CipR, and by 2000, 21 (10.4%) of 201 gonococcal isolates were CipR. Of the CipI/R gonococcal isolates tested for resistance to penicillin and tetracycline (minimum inhibitory concentration [MIC] $\geq 2.0 \mu\text{g/mL}$ of penicillin or tetracycline, respectively), 51 of 90 (57%) were resistant to penicillin (32 of 51 [63%] of these were penicillinase-producing *N. gonorrhoeae*), and 25 of 90 (28%) were resistant to tetracycline. All isolates tested had MICs $\leq 0.25 \mu\text{g/mL}$ of ceftriaxone, cefixime, and azithromycin; all isolates tested were susceptible (MIC $\leq 128.0 \mu\text{g/mL}$) to spectinomycin.

Case-Series Medical Record Review

From January 1990 to December 1999, 114 CipI or CipR gonococcal isolates were identified from laboratory records, 11 of which (8 CipI and 3 CipR) could not be linked to a person (Fig. 3). Of the 103 patients identified who met the case-patient definition, the medical record and/or interview forms completed by public health personnel were available for 88 (85%). In addition, the interview forms identified 3 presumptive case-patients.

Analysis of demographic data for case-patients showed that 70 (97%) of the 72 patients for whom zip code data were available were diagnosed with gonorrhea on the island of Oahu. Fifty (59%) of the case-patients were Asian/Pacific Islander and 20 (24%) were white (Table 1). The median age overall was 30 years (range, 16–53 years), with a median age of 31 years for male case-patients

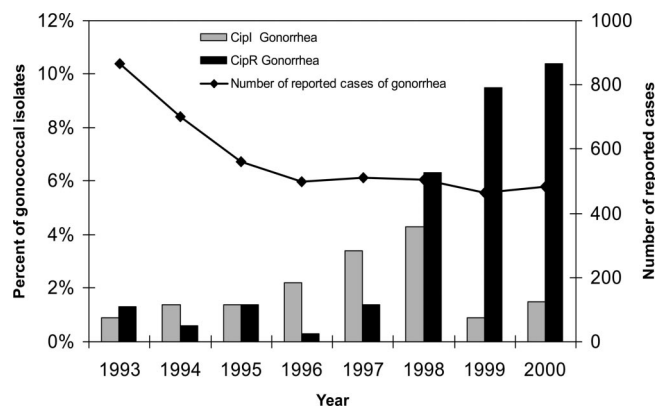


Fig. 2. Percent of gonococcal isolates that were ciprofloxacin resistant (CipR)^a or had intermediate resistance to ciprofloxacin (CipI)^b, and number of reported cases of gonorrhea, by year—Hawaii, 1993–2000. ^aCipR: *Neisseria gonorrhoeae* resistant to ciprofloxacin, minimum inhibitory concentration (MIC) $\geq 1.0 \mu\text{g/mL}$ by agar dilution, or disk diffusion zone size ≤ 27 mm. ^bCipI: *Neisseria gonorrhoeae* with intermediate resistance to ciprofloxacin, MIC of 0.125 to 0.5 $\mu\text{g/mL}$ by agar dilution, or disk diffusion zone size of 28–35 mm. From May 1994–2000, numbers reflect isolates identified by the Hawaii State Laboratory, Seattle Gonococcal Isolate Surveillance Project (GISP) Regional Laboratory or the CDC *Neisseria* Reference Laboratory. Before May 1994, numbers reflect isolates identified through the Seattle GISP Regional Laboratory or CDC *Neisseria* Reference Laboratory only.

and 24 years for female case-patients. Thirty-one (34%) of the case-patients were female; however, women were underrepresented because case-patients diagnosed before May 1994 were mainly identified through GISP, which only collects specimens from male patients.

Of the 78 patients with information in their medical records regarding medication use in the preceding 30 days, 9 case-patients (12%) admitted to recent antimicrobial use. Sixty-six case-patients had documentation indicating they were asked about foreign travel in the preceding 30 days or sex partner travel in the preceding 60 days. Thirty-three (50%) of these case-patients had a history of recent foreign travel or a sex partner with recent foreign travel. Male case-patients were significantly more likely to report foreign travel to Asia than female case-patients (26 of 47 vs. 2 of 18, $P < 0.005$).

Case-patients seen in a private clinic reported recent foreign travel or sex partner travel in Asia more often than case-patients seen in the STD Clinic. However, this difference did not reach statistical significance (13 of 19 vs. 20 of 47; $P = 0.06$). The case-patients seen in private clinics were significantly more likely to be female (20 of 34 vs. 11 of 57; $P < 0.0005$).

Sexually Transmitted Disease Clinic Medical Record-Based Case-Control Study

Fourteen patients from the case-series were diagnosed with gonorrhea at the STD Clinic between January 1, 1998, and September 30, 1999, and therefore met the case-patient definition for the case-control study. One hundred twenty-seven patients met the control-patient definition (Table 2). The case-patients and control-patients were similar regarding sex, coinfection with chlamydia, and other social characteristics as noted in Table 2.

Twelve (86%) of the case-patients and 117 (92%) of the control-patients had documentation on their medical record regarding foreign travel or a sex partner with recent foreign travel. Case-

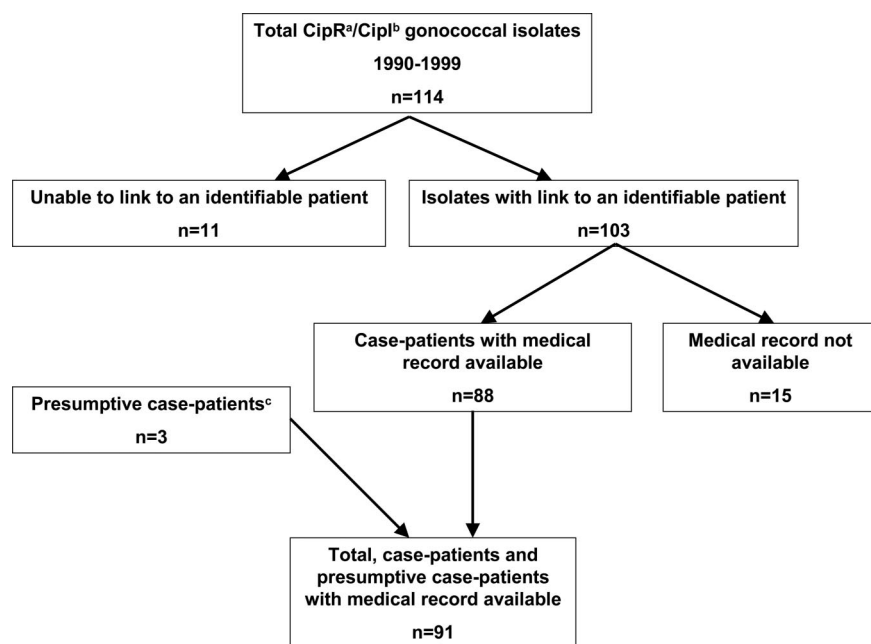


Fig. 3. Case ascertainment for patients with gonorrhea resistant to ciprofloxacin (CipR^a) or with intermediate resistance to ciprofloxacin (CipI^b), Hawaii, 1990–1999. ^aCipR: *Neisseria gonorrhoeae* resistant to ciprofloxacin, minimum inhibitory concentration (MIC) ≥ 1.0 $\mu\text{g/mL}$ by agar dilution, or disk diffusion zone size ≤ 27 mm. ^bCip I: *Neisseria gonorrhoeae* with intermediate resistance to ciprofloxacin, MIC of 0.125 to 0.5 $\mu\text{g/mL}$ by agar dilution, or disk diffusion zone size of 28–35 mm. ^cPresumptive case patient is defined as a person identified as a direct sexual contact of a CipR/CipI patient, who tested positive for gonorrhea within 14 days of the CipR/CipI patient's diagnosis, but when resistance testing was not done.

patients were significantly more likely than control-patients to have recently traveled in Asia or to have a sex partner who recently traveled in Asia. Although neither of the 2 female case-patients

reported recent foreign travel, 1 reported a sex partner who traveled to Korea. Among those reporting no foreign exposure, case-patients were significantly more likely to be Filipino (4 of 6 vs. 13

TABLE 1. Medical Record Review: Characteristics of Patients Diagnosed With Laboratory-Confirmed (n = 88) or Presumptive* (n = 3) CipI[†] or CipR[‡] Gonorrhea in Hawaii, January 1, 1990, to December 31, 1999

	Overall (n = 91)	STD Clinic (n = 57)	Private Clinics (n = 34)
Female case-patients	31 (34%)	11 (19%)	20 (59%)
Median age, years (range)	30 (16–53)	30 (16–53)	28 (16–49)
Race/ethnicity			
White	20/85 (24%)	15/55 (27%)	5/30 (17%)
Black	6/85 (7%)	6/55 (11%)	0/30 (0%)
Asian/Pacific Islander	50/85 (59%)	28/55 (51%)	22/30 (73%)
Filipino	15/50 (30%)	7/28 (25%)	8/22 (36%)
Chinese	9/50 (18%)	4/28 (14%)	5/22 (23%)
Japanese	8/50 (16%)	5/28 (18%)	3/22 (14%)
Hawaiian	6/50 (12%)	3/28 (11%)	3/22 (14%)
Korean	5/50 (10%)	5/28 (18%)	0/22 (0%)
Other ethnicity	7/50 (14%)	4/28 (14%)	3/22 (14%)
Other	9/85 (11%)	6/55 (11%)	3/30 (10%)
Not documented	6	2	4
Heterosexual	53/58 (91%)	46/50 (92%)	7/8 (88%)
Median no. of sex partners§ (range)	1.0 (0–3)	1.0 (0–2)	1.0 (0–3)
History of previous STD	29/68 (43%)	22/52 (42%)	7/16 (44%)
Coinfected with chlamydia	8/46 (17%)	4/25 (16%)	4/21 (19%)
Recent§ antimicrobial use	9/78 (12%)	6/53 (11%)	3/25 (12%)
Recent foreign exposure in Asia	33/66 (50%)	20/47 (43%)	13/19 (68%)

Denominators are listed when number of patients with available information is less than the total number interviewed and represent number of patients for whom data were available for given characteristic.

*A presumptive CipR/CipI patient is defined as a person identified as a direct sexual contact of a CipR/CipI patient who tested positive for gonorrhea within 14 d of the CipR/CipI patient's diagnosis but when resistance testing was not done.

†CipI: Gonorrhea with intermediate resistance to ciprofloxacin, defined as minimum inhibitory concentration (MIC) of 0.125–0.5 $\mu\text{g/mL}$ by agar dilution or disk diffusion zone size of 28–35 mm.

‡CipR: Gonorrhea resistant to ciprofloxacin, defined as minimum inhibitory concentration ≥ 1.0 $\mu\text{g/mL}$ by agar dilution or disk diffusion zone size ≤ 27 mm.

§Prior 30 days.

||Recent foreign exposure is defined as travel within the last 30 d or a sex partner with foreign travel in the last 60 days.

STD = sexually transmitted disease.

TABLE 2. STD Clinic Medical Record-Based Case-Control Study: Characteristics of Case-Patients With CipI* or CipR† Gonorrhea and Control-Patients With Ciprofloxacin-Susceptible Gonorrhea Seen at the STD Clinic in Honolulu, Hawaii, January 1, 1998, through September 30, 1999

	Case-Patients (n = 14)	Control-Patients (n = 127)	P Value
Diagnosed in 1998	6 (43%) [3 CipI/3 CipR]	81 (64%)	
Diagnosed in 1999 (January–September)	8 (57%) [1 CipI/7 CipR]	46 (36%)	
Median age, years (range)	34 (20–53)	25 (14–57)	
Female	2 (14%)	43 (34%)	
Race/ethnicity			
Asian/Pacific Islander	6/13 (46%)	44/126 (35%)	
Filipino	4/13 (31%)	14/126 (11%)	
Hawaiian	1/13 (8%)	5/126 (4%)	
Japanese	1/13 (8%)	11/126 (9%)	
Black	0/13 (0%)	40/126 (32%)	0.02
White	6/13 (46%)	30/126 (24%)	
Native American/Alaska Native	1/13 (8%)	0/126 (0%)	
Homosexual/bisexual	1/14 (7%)	26/125 (21%)	
Median no. of sex partners‡	1.0 (range, 1–3)	1.0 (range, 0–20)	
History of previous STDs	6 (43%)	50 (39%)	
History of previous gonorrhea	4 (29%)	41 (32%)	
Recent‡ antimicrobial use	3/14 (21%)	4/124 (3%)	0.02
No. of patients questioned regarding recent foreign exposure§	12 (86%)	117 (92%)	
No. of patients with recent foreign exposure§			
in Asia	6/12 (50%)	10/117 (9%)	0.0008
Foreign travel to Asia	4/12 (33%)	8/117 (7%)	0.01
Sex partner who recently traveled to Asia	2/12 (17%)	2/117 (2%)	0.04
Not documented	2/14 (14%)	10/127 (8%)	

P values presented only when statistically significant.

Denominators are listed when number of patients with available information is less than the total number interviewed and represent number of patients for whom data were available for given characteristic.

*CipI: Gonorrhea with intermediate resistance to ciprofloxacin, defined as minimum inhibitory concentration (MIC) of 0.125–0.5 µg/mL by agar dilution or disk diffusion zone size of 28–35 mm.

†CipR: Gonorrhea resistant to ciprofloxacin, defined as MIC ≥1.0 µg/mL by agar dilution or disk diffusion zone size of ≤27 mm.

‡Prior 30 days.

§Recent foreign exposure is defined as travel within the 30 days before diagnosis of gonorrhea or a sex partner with foreign travel in the last 60 days.

STD = sexually transmitted disease.

of 107; $P < 0.01$). There were 2 case-patients with no documentation on their medical record regarding foreign travel or sex partner travel. One of these case-patients was identified as “Hawaiian/Chinese”; the other was “Japanese/Hawaiian/Portuguese.” Case-patients were also significantly more likely to have been using antimicrobials in the 30 days before their gonorrhea diagnosis. The antimicrobials reported by the 3 case-patients were erythromycin, levofloxacin, and an unspecified antimicrobial.

Sexually Transmitted Disease Clinic Prospective Case-Control Interviews

From January to December 2000, 9 case-patients with CipR *N. gonorrhoeae*, 2 case-patients with CipI *N. gonorrhoeae*, and 52 control-patients with gonorrhea not determined to be CipR or CipI were seen at the Hawaii STD Clinic (Table 3). Case-patients and control-patients were similar regarding sex, sexual orientation, and other social characteristics as noted in Table 3.

Case-patients with CipI/R *N. gonorrhoeae* were significantly more likely to be Asian/Pacific Islander than were control-patients with isolates susceptible to ciprofloxacin. In addition, case-patients were significantly more likely to report foreign travel in the prior 30 days. However, 7 (70%) of the 10 case-patients who were asked specifically denied recent foreign travel or a sex partner with recent foreign travel. Case-patients who reported no recent travel or sex partner travel were more likely to be Hawaiian or Filipino

than were control-patients who reported no recent travel or sex partner travel (6 of 7 vs. 11 of 49; $P < 0.005$).

Discussion

The first CipR gonococcal isolate identified in the United States was from a patient in Hawaii in 1991.⁶ From 1993 to 1998, the percentage of gonococcal isolates from Hawaii that were CipI increased slowly, with a subsequent decrease in 1999 and 2000 for reasons that are not clear. There were no methodologic changes in testing or reporting practices identified that would account for this decrease. Interestingly, in the Philippines, a similar decrease in the number of CipI *N. gonorrhoeae* isolates appeared to occur between 1994 and 1996.⁸ During each year from 1993 to 1997, less than 1.5% of gonococcal isolates in Hawaii were CipR. However, as identified in this investigation, the percentage of gonococcal isolates that were CipR increased steadily from 1998 to 2000, at which point 10.5% of gonococcal isolates from Hawaii were CipR. Given Hawaii's geographic proximity to Asia, it is not surprising that this was the first place in the United States where increased prevalence of CipR *N. gonorrhoeae* was identified. In 1994, of the Asian countries submitting gonococcal isolates to the WHO Western Pacific Gonococcal Antimicrobial Surveillance Programme (GASP), less than 7% from any country were CipR.⁹ By 1999, 53% or more of gonococcal isolates submitted to GASP from

TABLE 3. STD Clinic Prospective Case–Control Interviews: Characteristics of Case-Patients With CipI* or CipR† Gonorrhea and Control-Patients With Ciprofloxacin-Susceptible Gonorrhea Seen at the STD Clinic in Honolulu, Hawaii, January 1, 2000, through December 31, 2000.

Characteristic	Case-Patients (n = 11)	Control-Patients (n = 52)	P Value
No. with CipR <i>N. gonorrhoeae</i>	9	N/A	
No. with CipI <i>N. gonorrhoeae</i>	2	N/A	
Median age (range)	30 y (16–28)	24 y (15–53)	
Female	3 (27%)	12 (23%)	
Male	8 (73%)	40 (77%)	
Race			
Asian/Pacific Islander	10 (91%)	29 (56%)	0.04
Black	0	13 (25%)	
White, non-Hispanic	1 (9%)	6 (12%)	
Other/unknown	0	4 (8%)	
Country of origin			
US/Hawaii	5/10 (50%)	16/43 (37%)	
US (other than Hawaii)	0	18/43 (42%)	0.01
Asia	5/10 (50%)	7/43 (16%)	0.04
(2 Philippines, 1 Japan, 1 Singapore, 1 Taiwan) (4 Philippines, 1 Micronesia, 1 Guam, 1 Marshall Islands)			
Other/unknown	0	2/43 (5%)	
Unknown	1 (9%)	9 (17%)	
Homosexual/bisexual	2 (18%) (males)	16 (31%) (15 males, 1 female)	
Median no. of sex partners‡ (range)	2 (1–5)	1 (0–6)	
Recent‡ antimicrobial use	2 (18%)	10 (19%)	
Recent foreign exposure§	3/10 (30%)	2/52 (4%)	0.03
Recent foreign travel	3/10 (30%)	2/52 (4%)	0.03
(1 China, 1 Japan, 1 Vietnam)		(2 Philippines)	
Sex partner with recent‡ foreign travel	0/5	0/24	
Military occupation	0	6/50 (12%)	
Military sex partner reported	1/10 (10%)	10/48 (21%)	
CSW personal exposure	0	1/47 (2%)	
Sex partner engaged in CSW	2/10 (20%)	6/49 (12%)	

P values presented only when statistically significant.

Denominators are listed when number of patients with available information is less than the total number interviewed and represent number of patients for whom data were available for given characteristic.

*CipI: Gonorrhea with intermediate resistance to ciprofloxacin, defined as minimum inhibitory concentration (MIC) of 0.125–0.5 µg/mL by agar dilution or disk diffusion zone size of 28–35 mm.

†CipR: Gonorrhea resistant to ciprofloxacin, defined as MIC ≥1.0 µg/mL by agar dilution or disk diffusion zone size of ≤27 mm.

‡Prior 30 days.

§Recent foreign exposure is defined as travel within the 30 d before diagnosis of gonorrhea or a sex partner with foreign travel in the last 60 days.

CSW = commercial sex worker; STD = sexually transmitted disease; N/A = not available.

China, Hong Kong, and the Philippines were CipR.³ Overall, the prevalence of CipR *N. gonorrhoeae* remains low for the mainland United States where they were first reported in 1995 from 1 patient in Colorado and 8 patients in Washington.¹⁰ In 2000, excluding gonococcal isolates from Hawaii, 0.2% of U.S. gonococcal isolates tested in GISP were CipR.⁵ However, in 2001, an increase in the prevalence of CipR *N. gonorrhoeae* isolates from California was noted; 43% of these infections were in patients who reported recent travel to Hawaii, the Pacific Islands, or Asia, or who reported having a sex partner who recently traveled to 1 of these locations.¹¹

Based on data from the medical record review of patients with CipI/R gonococcal isolates in Hawaii, during the 1990s, this form of gonorrhea occurred predominantly in heterosexual Asian/Pacific Islanders. Evidence from the medical record-based case-control study and the prospective interviews in 2000 suggests endemic transmission of CipI/R *N. gonorrhoeae* occurred frequently in Hawaii in 1999 and 2000. In 1998 and 1999, 50% of STD Clinic patients with CipI/R *N. gonorrhoeae* indicated that they had acquired their infection locally from a sex partner who had no recent travel. For 2000, 70% of patients with CipI/R *N. gonorrhoeae* in Hawaii denied recent foreign travel or sex partner travel, indicating that an increasing percentage of these resistant

infections were being endemically transmitted in Hawaii. Epidemiologic findings for 1998–1999 indicate that patients with CipI/R *N. gonorrhoeae* who denied recent foreign exposure were more likely to report being Filipino. In 2000, those with CipI/R *N. gonorrhoeae* who denied recent foreign travel or sex partner travel were equally likely to be Hawaiian as Filipino and significantly more likely to be 1 of these 2 ethnicities than control-patients. This suggests a possible change in the communities most affected by this resistant form of *N. gonorrhoeae*. An attempt was made to correlate strain typing of the isolates with epidemiologic linkages identified in this investigation with limited success. However, the overall molecular epidemiology of the *N. gonorrhoeae* isolates suggests possible endemic transmission as well. In 1999, among the isolates collected from these case-patients, for the first time, clusters of phenotypically identical *N. gonorrhoeae* isolates were identified from Hawaii, with fewer overall strain phenotypes being identified compared with earlier years.⁷ The most prevalent quinolone resistance-determining region alteration patterns identified among these *N. gonorrhoeae* isolates was also the most prevalent pattern among CipR *N. gonorrhoeae* isolates tested from the Philippines from 1994 and 1996.

There are limitations to this investigation of CipI/R *N. gonorrhoeae*

in Hawaii. Incomplete laboratory data are available for years before 1994, and the numbers of patients with resistant *N. gonorrhoeae* available for the case-control studies in 1998–2000 are relatively small. This is partially the result of the relatively low rate of gonorrhea infections in Hawaii, but is also because approximately 50% of gonorrhea infections in Hawaii during the study period were diagnosed by nonculture tests and therefore no antimicrobial susceptibility testing could be done. It is likely that the percent of gonococcal infections in Hawaii caused by CipI/R *N. gonorrhoeae* presented here is an underestimate. The military and many private practitioners use nonculture tests for gonorrhea diagnosis. From the case-series comparison of case-patients seen at private versus public clinics, private clinic patients were more likely to have traveled abroad. In addition, United States military personnel may be more likely to have recent foreign travel. Therefore, 2 populations who are more likely to travel are less likely to be diagnosed with gonorrhea by culture and, as a result, are underrepresented. The fact that the 2 case-control studies were performed at the STD Clinic is also a limitation because this population is not representative of all patients with gonorrhea in Hawaii. From the case-series medical record review, case-patients diagnosed with CipI/R *N. gonorrhoeae* at the STD Clinic were less likely to be female (19% vs. 59%) and less likely to report recent foreign travel (43% vs. 68%) than those diagnosed at private clinics. As a result, however, STD Clinic patients may be more representative of those acquiring CipI/R *N. gonorrhoeae* locally in Hawaii.

The finding during this investigation that 50% of gonorrhea infections in Hawaii in 1999 were diagnosed by nonculture methods is consistent with changes in diagnostic testing practices occurring throughout the United States. Although these nonculture tests are easier to collect, requiring only a urine sample, they pose a new challenge to monitoring antimicrobial resistance among *N. gonorrhoeae* isolates. As demonstrated by this investigation, it is important for public health laboratories to maintain the capacity to perform culture and antimicrobial susceptibility testing for *N. gonorrhoeae*. Monitoring resistance patterns among *N. gonorrhoeae* isolates by local health departments is important to assist with local gonorrhea treatment recommendations and control efforts. Providers seeing patients with these infections should be aware of local patterns of drug resistance in *N. gonorrhoeae* isolates and modify their treatment practices for gonorrhea as necessary. This is particularly important for female patients. Compared with men, women with gonorrhea are much more likely to be asymptomatic and more frequently develop serious, potentially life-threatening sequelae. Such complications are of particular concern if they are treated with an antimicrobial to which the gonococcal isolate is not susceptible. When providers identify a possible gonorrhea treatment failure, a gonococcal culture should be obtained from the patient and submitted to the local public health laboratory for susceptibility testing.

During the early 1990s, the number of gonorrhea cases per year in Hawaii steadily declined. From 1996 to 2000, the number of cases per year stabilized at approximately 500 per year. Inexpensive, highly effective gonorrhea treatment is necessary to achieve further decreases in the number of gonorrhea infections. With the increase in CipR *N. gonorrhoeae* in Hawaii, there are now fewer treatment options for gonorrhea. Fluoroquinolone antimicrobials such as ciprofloxacin, ofloxacin, and levofloxacin are no longer recommended treatment for gonorrhea infections acquired in Hawaii, Asia, or the Pacific Islands or for those who may have acquired their infection from a sex partner who recently traveled to these locations.¹² As a result of the reported increase in CipR *N. gonorrhoeae* isolates in California and other locations, and the increase identified among men who have sex with men (MSM) in the United States in 2003, fluoroquinolones are no longer recom-

mended to treat MSM with gonorrhea in the United States, or any patient who has acquired gonorrhea in CipR endemic areas.^{11,13} For these patients, cefixime, ceftriaxone, or spectinomycin is recommended. All 3 of these antimicrobials are more expensive than ciprofloxacin. Also, spectinomycin is not effective against pharyngeal gonococcal infections. In countries where spectinomycin had been used widely, resistance in *N. gonorrhoeae* developed relatively rapidly.¹⁴ Other effective antimicrobials are not currently recommended because of their expense, side effects, or requirement for parenteral administration. Resistance to penicillin and tetracycline in these CipR gonococcal isolates remains high, precluding effective use of these older antimicrobials to treat gonorrhea infections. It is important to continue closely monitoring antimicrobial resistance patterns for *N. gonorrhoeae* to modify gonorrhea treatment regimens appropriately.

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